U.S.S.N. 09/526,582
Filed: March 16, 2000
RESPONSE TO OFFICE ACTION

Remarks

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 19 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Claim 19 has been amended to more clearly define the antibodies to the apolipoprotein as a first reagent (in a first reagent container) and the antibodies to the albumin as a second reagent (in a second reagent container), not as a single mixed antibody solution. Antibodies to albumin are used to correlate the concentration of proteins in the saliva and serum as described on pages 19-20 of the specification.

Claim 19 is different than claim 17. Claim 17 further defines the kit of claim 16 by defining reagents for the detection of antibody-apoliprotein complexes. These reagents are described on page 12-13 of the specification and include for example secondary antibodies labeled with fluorescent and enzymatic markers. The anti-albumin antibodies of claim 19 bind to albumin, not antibody-apolipoprotein complexes.

Rejection Under 35 U.S.C. § 103

Claims 1-3, 5-7, 10-14, 16-18, and 20-22 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 to Oberhardt ("Oberhardt '991"), in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and U.S. Patent No. 6,291,178 to Schneider ("Schneider").

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RESPONSE TO OFFICE ACTION

Claims 1 and 4 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,210,906 to Kundu et al. ("Kundu"), in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and U.S. Patent No. 6,291,178 to Schneider ("Schneider").

Claims 8, 9, 15 and 19 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 to Oberhardt ("Oberhardt '991"), in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman"), and U.S. Patent No. 6,291,178 to Schneider ("Schneider"), and in further view of Fisher et al. (Diabetes Res. Clin. Practice, 11(2), 117-119 (1991) ("Fisher") and Coppo et al. (J.Diabetic Complications, 1987) ("Coppo"). These rejections are respectfully traversed.

The Legal Standard for Obviousness

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q.

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1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "**question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.** *WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

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It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Furthermore, the "prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). (Emphasis in original)

The Claimed Invention

Claim 1 is drawn to a method for determining the level of an apolipoprotein in the serum of an individual based on levels of the apolipoprotein in the individual's saliva comprising

(1) obtaining a saliva sample from an individual,

(2) reacting the apolipoproteins in the saliva sample with antibodies immunoreactive with one or more of the apolipoproteins,

(3) wherein the antibodies are in a quantitative assay which measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith,

(4) determining the amount of apolipoproteins in the serum of the individual by comparing the immunoreactivity between the antibodies and apolipoproteins in the saliva sample by reference to standards of known amounts of apolipoproteins in saliva and serum.

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As discussed below, the prior art fails to teach each of the claimed elements. The prior art also fails to teach the most important element that would lead one skilled in the art to combine the elements with a reasonable expectation of success: *that the level of apolipoprotein in saliva is proportional to the level of apolipoprotein in serum.* The examiner has cited no art that discloses or makes obvious this fact.

The Prior Art

The prior art does not disclose each claimed element. In particular, the prior art fails to disclose at least one critical element - that saliva apolipoprotein levels can be correlated with serum apolipoprotein levels.

Oberhardt '133 and Oberhardt '991

The examiner has cited Oberhardt '991 and '133 for the purpose of showing that one can monitor magnetic particle response to determine the concentration of apolipoprotein in a sample, which may be saliva.

Oberhardt '991 discloses a method and a system of dry chemistry cascade immunoassay and affinity assay. Neither Oberhardt patent discloses the correlation between apolipoprotein levels in saliva and blood. Neither of these patents enables one of ordinary skill to detect the levels of lipoproteins in saliva and extrapolate to the serum concentrations.

Dependent claims require removal of mucopolysaccharides from the saliva sample. These patents provide no description of saliva collection, removal of mucopolysaccharides, or reason to remove mucopolysaccharides.

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Fellman

The examiner has relied upon Fellman for showing that saliva can be collected.

Fellman discloses a means for reducing the viscosity of a body fluid sample such as saliva which contains mucopolysaccharides, using a cationic quaternary ammonium reagent. Fellman does not disclose detecting apolipoproteins in saliva with antibodies, or that the levels can be correlated with levels in serum. Fellman does not disclose a quantitative assay kit comprising collection mean, antibodies to apolipoprotein, and means to compare saliva and serum apolipoprotein levels.

Kundu

The examiner has relied upon Kundu for the detection of apolipoprotein A in a saliva sample by reacting monoclonal antibodies with the apoliprotein (col. 4, lines 39-52 and col. 8, lines 8-15). Certainly col. 4 refers to reaction of an antibody with a protein in a sample containing an apolipoprotein, but there is no mention of saliva. Col. 8 does refer to samples as including saliva.

Kundu discloses specific antibodies to Apo A and methods to use the antibodies. Similar to the Oberhardt patents, Kundu does not disclose why or how the levels of apolipoproteins should be detected in saliva, nor how to correlate the levels of the apolipoproteins in the saliva with the levels of the apolipoproteins in the serum, as defined by the claims. Kundu does not disclose removal of mucopolysaccharides, or reasons to remove mucopolysaccharides.

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Schneider

Schneider '178 is cited by the examiner as "teaching that it is known in the art to correlate a saliva sample with a blood sample to determine an amount of analyte of interest."

Schneider '178 has a filing date only of August 30, 1999, relating to apolipoprotein in saliva, and is therefore not available as of prior art. Should the examiner insist upon relying on Schneider, he must rely on ***the priority application, which issued as U.S. Patent No. 5,968,746. It is well established that a patent is only awarded priority for what is disclosed in the earlier application, not later added subject matter.***

The examiner has acknowledged that Schneider's earlier priority application, filed November 26, 1997, now U.S. Patent No. 5,968,746, fails to disclose the correlation between apolipoprotein levels in saliva and apolipoprotein levels in serum. As the examiner explicitly notes, Schneider includes not only the measurement of drugs but also proteins, citing to col. 2, line 43, claims 6 and 13.

Claims 6 and 13 of U.S. Patent No. 5,968,746 depend from claim 1. Claim 1 is drawn to an assay sample collection kit for measurement of a hydrophilic compound. The hydrophilic compound is defined in the specification as one which is absorbed from the intestinal tract into the bloodstream and is found either in the administered form or as a metabolite thereof (col. 2, lines 31-37).

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Apolipoprotein does not fall within the scope of this definition. Therefore, to the extent the examiner is relying on '746 patent for priority, there is no disclosure prior to the filing date of this application, of a correlation in levels of apolipoprotein in serum and in saliva.

Fisher and Coppo

The examiner has relied on Fisher and Coppo for "normalizing the amount of apolipoprotein to the amount of albumin present in the saliva sample and antibodies immunoreactive to albumin in the device or kit for determining apolipoprotein concentration."

Fisher and Coppo provide assays for detecting albumin, one in saliva and one in urine. Neither suggest detecting apolipoprotein in saliva, nor that the levels could be correlated with the levels in the serum by measuring the values of the albumin.

Factual Analysis

Oberhardt in combination with Fellman and Schneider

Although it was postulated that apolipoproteins were present in saliva, it was not previously known that the levels could be correlated to serum levels, thereby making a non-invasive test using saliva a possibility. The Applicants have demonstrated the correlation between levels of apolipoproteins in saliva and levels of HDL and LDL in serum.

As described above, Oberhardt is deficient in detecting apolipoprotein levels, correlating the levels of apolipoprotein in blood and saliva as well as collecting and preparing a saliva sample for assay. Fellman discloses a method to remove mucopolysaccharides in a saliva sample for detection of an analyte. Fellman does not disclose detection of apolipoprotein or the

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quantitiative correlation of apolipoprotein levels between saliva and serum. Schneider does not make up for these deficiencies.

Schneider is a qualitative, not a quantitative, assay to detect hydrophilic compounds. This is a major difference. It is also why Schneider's system provides for extensive dilution of sample – which may alter the amount of apolipoprotein measured in a given volume, thereby completely destroying one's ability to correlate the levels of apolipoprotein measured in the sample with the levels measured in the serum. Second, Schneider's system is primarily drawn to measurements of other molecules, such as ethanol, which are known to have a correlation between saliva levels and serum levels, unlike in the present case.

Schneider discloses that hydrophilic compounds can be detected in saliva and mentions hydrophilic proteins (col 2, line 41). Apolipoprotein is not a hydrophilic protein. The carboxy terminal part of the protein is hydrophobic. The mixed nature of apolipoprotein accounts for the ability of apolipoprotein to bind lipids. The disclosure of Schneider clearly states that their method is not appropriate for non-hydrophilic proteins. One would not be motivated to use the method of Schneider to examine proteins with hydrophobic properties.

It is also significant that Schneider did not include apolipoproteins in the '178 patent specification and added reference to apolipoprotein in the subsequent CIP application filed August 30, 1999. This is because it was not known prior to filing the CIP that apolipoprotein could be correlated between saliva and serum. This element is not taught in any of the cited

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references. One of skill in the art would not be motivated to use the disclosure of Schneider to detect apolipoprotein in saliva absent the teachings and examples of the present specification.

Schneider also discloses that excretion of protein by parenchymal cells into the saliva is hindered by the presence of enzymes that degrade the proteins into peptides and amino acids (col 2, line 62 to col 3,line 16). The presence of aminopeptidases and hydrolysis of peptides in saliva is well known in the art. In a *quantitative* assay such as the one claimed, degradation of the target is a serious problem. It would be highly problematic for obtain a quantitative concentration and correlation to serum concentrations of a protein that was easily degraded. Applicants teach preservation of the saliva sample on page 10, lines 18-22 by refrigerating the sample, adding protease inhibiting enzymes and testing the sample for the analyte within 3 hours of collection before major degradation can occur. One of skill in the art would not have expected a correlation between serum and saliva apolipoprotein levels using the method of Schneider because of the degradation of salivary proteins. The method of Schneider is effective for detecting the presence of drugs that are not degraded by proteolytic enzymes or even detecting the presence of proteins in saliva. Based on the teachings of Schneider, one of skill would know that the lack of protein preservation in their method of Schneider would render a correlation totally impossible. Schneider does not disclose that saliva apolipoprotein levels can be correlated with serum apolipoprotein levels. Schneider provides no teaching or example that apolipoproteins can be detected using their method and discloses that it is likely not possible.

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Conversely, Applicant's have demonstrated that despite the negative teachings of Schneider, it is possible to read the concentration of apolipoprotein in a saliva sample and correlate it to serum apolipoprotein levels. Despite the negative teachings of Schneider, the Applicant's have obtained unexpected results showing that degradation of the salivary apolipoprotein can be controlled and quantitative data can be obtained which can be correlated to serum apolipoprotein levels.

In view of the above discussion, Oberhardt in combination with Fellman and Schneider neither discloses or makes obvious the claimed method. One of skill in the art would not be motivated to combine these references to obtain a quantitative assay for apolipoprotein in view of the lack of guidance and the negative teachings of Schneider.

Kundu, Fellman and Schneider in combination

Kundu discloses antibodies to Apo A and methods to use these antibodies. Kundu does not teach a quantitative assay to detect Apo A in saliva and correlate it to serum Apo A concentrations. Fellman teaches a method to remove mucopolysaccharides from saliva to prepare a saliva sample for assay but no suggestion to detect apolipoproteins or correlate with serum levels. As discussed above, Schneider does not provide the necessary guidance to make up for these deficiencies. Schneider discloses a qualitative assay to detect hydrophilic compounds in saliva and discloses that protein detection is problematic because of degradation by salivary proteases. One of skill in the art would not be motivated to combine these references absent the teachings of the present specification with any expectation of success.

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The teachings and examples of the present specification make up for the deficiencies of Kundu, Fellman and Schneider by teaching that a *quantitative* correlation can be determined between apolipoprotein levels in saliva and blood and that the saliva sample can be properly treated immediately after collection to prevent degradation of salivary proteins. These elements are not disclosed in part or in total by the cited references.

Oberhardt, Fellman, Schneider, Fisher and Coppo in combination

As discussed above, Oberhardt, Fellman and Schneider in combination do not render the claimed method obvious. Claims 8-9, 15 and 19 further define the method by normalizing the levels of apolipoprotein detected in saliva to known standards of albumin to correlate saliva and serum concentrations. Fisher and Coppo provide assays for detection of albumin in saliva and urine. Neither suggest detecting apolipoprotein in saliva or correlating with serum levels for quantitative assay of apolipoprotein levels. Fisher and Coppo fail to address the deficiencies of Oberhardt, Fellman and Schneider and do not provide sufficient motivation to use albumin standards to obtain quantitative results correlating the levels of apolipoprotein between saliva and blood.

The Applicants have developed a novel and unobvious non-invasive assay for detecting serum apolipoprotein levels. The cited references do not disclose all claim elements nor do they provide the necessary motivation and teaching to warrant combination to arrive at the claimed method to detect apolipoprotein. In combination, by the own statements of the examiner, the prior art teaches only:

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The examiner has cited Oberhardt '991 and '133 for the purpose of showing that one can monitor magnetic particle response to determine the concentration of apolipoprotein in a sample, which may be saliva.

The examiner has relied upon Fellman for showing that saliva can be collected.

The examiner has relied upon Kundu for the detection of apolipoprotein A in a sample that can be saliva by reacting monoclonal antibodies with the apoliprotein (col. 4, lines 39-52 and col. 8, lines 8-15).

Schneider '178 is cited by the examiner as "teaching that it is known in the art to correlate a saliva sample with a blood sample to determine an amount of analyte of interest."

The examiner has relied on Fisher and Coppo for "normalizing the amount of apolipoprotein to the amount of albumin present in the saliva sample and antibodies immunoreactive to albumin in the device or kit for determining apolipoprotein concentration."

In combination, the examiner has failed to cite any prior art that teaches there is a reasonable expectation that one could determine levels of apolipoprotein in saliva and correlate these levels to the levels of apolipoprotein in serum. The only way the examiner can reach this conclusion is from applicants' specification – and hindsight reconstruction is not permitted. 35 U.S.C. 103 requires that the claimed subject matter must be obvious from the cited art – i.e., that the elements are disclosed and one skilled in the art is provided with the motivation to combine as applicants have done, with a reasonable expectation of success. There is no ***prior art*** that

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would lead one skilled in the art to this conclusion. Indeed, the prior art Schneider actually ***teaches away*** from such a conclusion.

Allowance of claims 1-22 is respectfully solicited.

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Respectfully submitted,

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I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, September 1, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Alexandria, Virginia 22313-1450.

Jean Hicks

Date: September 1, 2003

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